UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/458,905	12/10/99	FISHER C	X-12448

HM12/0518

ELI LILLY AND COMPANY
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INDIANAPOLIS IN 46285

EXAMINER	
RAO, M	

ART UNIT	PAPER NUMBER
1652	3

DATE MAILED: 05/18/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/458,905	Fisher et al.
Examiner	**Group Art Unit**
Manjunath Rao	1652

☒ Responsive to communication(s) filed on *Dec 10, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-20* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-20 are now pending and present for examination.

Claim Objections

2. Claims 4 and 14 are objected to because of the following informalities: Claims 4 and 14 recite dosage levels as micrograms/kg/hr. Applicants appear to refer to the body weight of the patients in "kg" . If so, appropriate correction is required.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glas-Greenwalt et al. (J. Lab Clin. Med., 1986, Vol. 108:415-422) in view of Grinnell et al. (Bio/Technology, 1987, Vol.5:1189-1192) and Gruber et al. (Circulation, 1990, Vol. 82:578-585). Claims 1-5 in this instant application are drawn to a method of treating a patient suffering from thrombotic thrombocytopenic purpura (TTP) comprising the administration of a pharmaceutically effective amount of protein C. Glas-Greenwalt et al. teach the characteristics of TTP disorder in terms of blood bio-chemistry and physiology with respect to plasma fibrinolysis and protein C. The

reference also teaches that protein C antigens were low in three of the six patients studied. However, the reference does not teach recombinant human protein C nor its use in treatment of TTP.

Grinnell et al. teach a method for preparation of recombinant human protein C and also show that it is several times more active than the plasma-derived human protein C.

Gruber et al. teach the inhibition of thrombus formation which is very similar to conditions of TTP (a platelet dependent thrombosis) by activated human recombinant protein C in a primate model of arterial thrombosis using baboons as model. The reference also teaches the methods of administering recombinant protein C in a pharmaceutical composition as a continuous infusion at a specific dosage. The reference also teaches that recombinant human activated protein C, like the human plasma derived plasma-derived activated protein C inhibited the thrombus formation.

Thus, it would have been obvious to one skilled in the art at the time the invention was made to combine the teachings of Glas-Greenwalt et al. with that of Grinnell et al. and Gruber et al. to develop a method of treatment for TTP using recombinant human protein C. Grinnell et al. teach that one would be motivated to do this in order to develop and use protein C as antithrombotic agent for use in septic shock and stroke and to prevent reocclusion in patients treated with fibrinolytic agents. One would also be motivated to develop and use a recombinant protein C as natural protein C is manufactured from donated blood plasma which is usually in short supply and also to avoid contamination of the final protein C product with potential

bacterial or viral pathogens. One would have a reasonable expectation of success since Glas-Greenwalt et al. teach that protein C antigens levels were low in three out of six TTP patients and Gruber et al. teach that recombinant activated protein C, like human plasma derived activated protein C, inhibited thrombus formation in a primate model clinical trial. Finally, Grinnell et al. teach a reliable and time-tested method for making recombinant human protein C.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to have performed the claimed invention.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 6-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glas-Greenwalt et al. (J. Lab Clin. Med., 1986, Vol. 108:415-422) in view of Grinnell et al. (Bio/Technology, 1987, Vol.5:1189-1192) and Gruber et al. (Circulation, 1990, Vol. 82:578-585) as applied to claims 1-5 above, and further in view of Hollenbeck et al. (Nephrol. Dial. Transplant., 1998, Vol. 13:76-81). Claims 6-20 are drawn to a method of treatment of TTP and

hemolytic uremic syndrome (HUS) conditions comprising administering either as a bolus injection or as a continuous infusion, a pharmaceutically effective amount of activated protein C at a specific dosage level (claims 6-10) and to a method of treating a patient with hemolytic uremic syndrome (HUS) conditions comprising administering either as a bolus injection or as a continuous infusion, a pharmaceutically effective amount of activated protein C at a specific dosage level (claims 11-20). Glas-Greenwalt et al., Grinell et al. and Gruber et al. were discussed above. Hollenbeck et al. teach that both TTP and HUS are characterized by similar outcomes such as microangiopathic hemolytic anemia, thromobocytopenia, and functional impairment of various organs and that there is considerable overlap between the clinical pictures and morphological findings of both disorders. The reference also teaches that case reports and more recent prospective studies indicate that the prognosis is favorably influenced by therapy with plasma exchange. It is also well known in the art that plasma is source of protein C and activated protein C.

Thus, it would have been obvious to one skilled in the art to combine the teachings of Glas-Greenwalt et al. (J. Lab Clin. Med., 1986, Vol. 108:415-422) in view of Grinnell et al. (Bio/Technology, 1987, Vol.5:1189-1192) and Gruber et al. (Circulation, 1990, Vol. 82:578-585) with that of Hollenbeck et al. and develop a method of either treating both TTP and HUS disorders or just the HUS disorder, which normally occurs in individuals with transplanted organs such as kidneys, using recombinant human protein C and recombinant activated human protein C.

Conclusion

5. No claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 6:30 a.m. to 3:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Manjunath N. Rao

May 17, 2000